tion of reproductive functions such as blockade of ovulation in the rat (*34*), dysmenorrhea in women (*11–15*), or altered androgen secretion in males (*16, 17*) may yield new insights into the causes of infertility during exposure to stressful circumstances. Additionally, in view of the anorexic (*34*) and antireproductive (*24*) effects of CRF, it is tempting to consider a pathogenic role of CRF in anorexia nervosa—a disorder often associated with activation of the hypothalamic-pituitary-adrenal axis (*35*).

REFERENCES AND NOTES

1. J. J. Christian, *Biol. Reprod.* **4**, 248 (1971).
2. J. S. Euker, J. Meites, G. D. Riegle, *Endocrinology* **96**, 85 (1975).
3. L. Krulich, E. Hefco, P. Illner, C. B. Read, *Neuroendocrinology* **16**, 293 (1974).
4. L. G. Nequin, J. A. Alvarez, C. S. Campbell, *Endocrinology* **97**, 718 (1975).
5. C. A. Blake, *Proc. Soc. Exp. Biol. Med.* **148**, 813 (1975).
6. R. W. Rhees and D. E. Fleming, *Physiol. Behav.* **27**, 879 (1981).
7. S. Plas-Roser and C. Aron, *ibid.*, p. 261.
8. G. Charpenet *et al.*, *Endocrinology* **109**, 1254 (1981).
9. Y. Tache, P. Du Ruisseau, J. R. Ducharme, R. Collu, *Neuroendocrinology* **26**, 208 (1978).
10. G. D. Gray *et al.*, *ibid.* **25**, 247 (1978).
11. E. R. Baker, *Fertil. Steril.* **36**, 691 (1981).
12. R. E. Frish, G. Wyshak, L. Vincent, *N. Engl. J. Med.* **303**, 17 (1980).
13. D. V. Harris, *Physician Sportsmed.* **6**, 24 (1978).
14. H. Ronkainen, A. Pakarinen, P. Kirkinen, A. Kauppila, *J. Clin. Endocrinol. Metab.* **60**, 416 (1985).
15. B. A. Bullen *et al.*, *N. Engl. J. Med.* **312**, 1349 (1985).
16. A. Nakashima, K. Koshiyama, T. Uozumi, Y. Monden, *Acta Endocrinol.* **78**, 258 (1975).
17. D. C. Cumming, M. M. Vickovic, S. R. Wall, M. R. Fluker, *J. Clin. Endocrinol. Metab.* **60**, 4 (1985).
18. J. M. Saez, A. M. Morera, F. Haour, D. Evain, *Endocrinology*, **101**, 1256 (1977).
19. D. M. Baldwin, *ibid.* **105**, 120 (1979).
20. D. R. Mann, G. G. Jackson, M. S. Blank, *Neuroendocrinology* **34**, 20 (1982).
21. T. H. Bambino and A. J. W. Hseuh, *Endocrinology* **108**, 2142 (1981).
22. N. Hagino, M. Watanabe, J. W. Goldzieher, *ibid.* **84**, 308 (1969).
23. D. M. Baldwin and C. H. Sawyer, *ibid.* **94**, 1397 (1974).
24. C. Rivier and W. Vale, *ibid.* **114**, 914 (1984).
25. P. M. Plotsky and W. Vale, *ibid.*, p. 164.
26. ———, *Neuroendocrinology*, in press.
27. M. Brown, Y. Tache, D. Fisher, *Endocrinology* **105**, 660 (1979).
28. C. Rivier *et al.*, *ibid.* **110**, 272 (1982).
29. J. Rivier, C. Rivier, W. Vale, *Science* **224**, 889 (1984). See figure 3 for the structures of r/hCRF, oCRF, and α-helical oCRF residues 9 to 41.
30. J. Rivier, J. Spiess, and W. Vale [*Proc. Natl. Acad. Sci. U.S.A.* **80**, 4851 (1983)] describe the methodology and give the structure of oCRF from which the structure of des-Glu[17] to Arg[35] can be deduced.
31. W. Vale *et al.*, in *Methods in Enzymology: Neuroendocrine Peptides*, P. M. Conn, Ed. (Academic Press, New York, 1983), pp. 565–577.
32. J. Buckingham, K. Dohler, C. Wilson, *J. Endocrinol.* **78**, 359 (1978); E. Smith, C. Bowers, J. Davidson, *Endocrinology* **93**, 756 (1973); R. Butcher, W. Collins, N. Fugo, *ibid.* **94**, 1704 (1974); A. Shaikh and S. Shaikh, *ibid.* **96**, 37 (1975).
33. T. Hiroshige and S. Wada-Okada, *Neuroendocrinology* **12**, 316 (1973).
34. D. R. Britton, G. F. Koob, J. Rivier, W. Vale, *Life Sci.* **31**, 363 (1982).
35. M. Hotta *et al.*, *J. Clin. Endocrinol. Metab.*, in press.

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Obesity, Overeating, and Rapid Gastric Emptying in Rats with Ventromedial Hypothalamic Lesions

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Measurements confirm the quantitative theoretical prediction that the autonomic nonendocrine abnormality of rapid daytime gastric emptying is the major primary cause of the obesity resulting from ventromedial hypothalamic lesions in rats. Therapy for obesity could include slowing of stomach emptying.

DESTRUCTION OF THE VENTROMEDIAL region (*1*) of the hypothalamus (VMH) in rats causes a syndrome characterized by a dynamic phase of increasing obesity, usually accompanied by hyperphagia. This is followed by a phase of static obesity when the total intake of food per day is more normal. During dynamic and static phases, the rat takes meals abnormally frequently during the light period of the day-night cycle (*2*).

Obesity and hyperphagia brought about by destruction of the VMH cannot be attributed to a deficit in satiety mechanisms. VMH lesions do not disrupt either the immediate satiating effects of food (*3*) or the parenteral satiety generated by the use of absorbed food carbohydrate for energy (*4, 5*). The VMH therefore is not the satiety center, mediating normal inhibition of feeding; yet the VMH receives information from the viscera (*6*) and contains neurons whose firing responds to their own glucose metabolism (*7*). Since these afferents do not directly inhibit feeding behavior, their function is presumably to modulate autonomic and perhaps hypophyseal outputs affecting the processing of food (*8*).

We have now found that VMH lesions disrupt autonomic output controlling the stomach and increase the normally slow daylight rate of gastric emptying of regular diet. We propose that the abbreviated satiating effect of food resulting from such gastric acceleration either is the sole primary cause of the obesity or is at least a quantitatively major primary cause along with other autonomic defects, such as insulin hypersecretion (*9*) and possibly reductions in fat mobilization (*10*) and thermogenic capacity (*11*). That is, the VMH syndrome is neither metabolic nor behavioral, and pair-feeding experiments (*12*) cannot be satisfactorily interpreted.

The experiments described here originated from our theory that eating motivation is physiologically controlled by the flow of readily used energy from absorption (*5, 13*). This theory provided the basis for quantitative explanations of feeding patterns and changes in body composition that were modeled by computer (*14*). The calculations showed that variations in the rate of gastric

Table 1. Rates of gastric emptying during early daylight in ventromedial hypothalamic and control rats (n = 6 to 8).

Stage	Gastric emptying rate (g hour^{-1})				Difference*
	VMH lesions		Sham-operated		
	Mean	SD	Mean	SD	
Four hours after lesions	0.54	0.04	0.42	0.09	$P < 0.01$
One week after lesions	0.69	0.08	0.43	0.03	$P < 0.01$
Dynamic obese phase	0.74	0.09	0.45	0.09	$P < 0.02$
Static obese phase	0.62	0.14	0.43	0.08	$P < 0.01$

*Calculated (t test) between VMH and sham-operated groups.

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Table 2. Characteristics of ventromedial hypothalamic and control rats (n = 6 to 8). Weight gain (in grams per day) was calculated for the 2 weeks after operation. Preference indicates whether oily chow was preferred to plain chow. Soluble gastric contents are reported as the percent dry weight. The satiety effect is the food-intake suppression (in grams) 2 hours after a 2-g starch load. NS, not significant.

Data	Weight gain	Preference (percent)	Soluble gastric contents	Satiety effect
		VMH lesions		
Mean	2.8	92	19	1.29
SD	1.7	17	8	0.44
		Sham-operated		
Mean	1.1	72	8	0.59
SD	0.3	25	3	1.10
Difference*	$P < 0.05$	$P < 0.01$	$P < 0.005$	NS

*Calculated (t test) between VMH and sham-operated groups.

emptying were sufficient to explain rats' nycthemeral feeding cycle of frequent meals by night and infrequent meals by day, as well as their episodic feeding (*14, 15*). One of the most striking predictions of the computer model (*5, 14*) was that the VMH syndrome is mainly attributable to loss of the normal daytime slowing of gastric emptying that occurs in intact rats (*16*).

The rate of gastric emptying of the maintenance diet was measured in the early part of the light phase (*17*), when it is normally at its slowest (*16*), 0.42 g hour^{-1} (n = 6 intact rats, SD = 0.08). Rapid daytime gastric emptying was evident when electrolytic lesions had been placed in the VMH (*1*) a few hours before the start of the gastric emptying test (Table 1). The gastric acceleration was also observed 1 week after surgery, in the dynamic phase at 4 to 6 weeks, and even after 11 to 12 weeks in the static phase (Table 1). The ratio of VMH to control rates closely approximated that postulated in the computer models to account for reported meal patterns and weight changes (*14*). Relative to control rats (in which electrodes had been lowered to the VMH but no current passed), these rats also showed the classic features of the VMH syndrome (Table 2): rapid weight gain (*18*), finickiness (*19*), and signs of gastric hypersecretion (*20*). Also, as in other studies (*5*), the VMH lesions did not disrupt the satiety produced by the use of food carbohydrate for energy after its intestinal absorption (Table 2).

The acceleration of gastric emptying as soon as lesions had been made indicates that this abnormality could be primary in the VMH syndrome. Basal insulin concentrations are not increased after VMH lesions (*21*). Observations of exaggerated insulin secretion early after VMH lesions (*22*) have been confounded by aftereffects of the faster emptying of food that may have been in the rat's stomach when the lesions were made. Cephalic-phase insulin secretion and secretion stimulated by intravenous glucose are attenuated when the VMH is inactivated by procaine (*23*). Thus, possibly all the well-known hypersecretion of insulin is secondary: faster gastric emptying produces faster absorption of nutrients across the intestinal wall (*16*); a persistent metabolic stimulus to the pancreatic β cell causes hypertrophy (*24*), which could result in hypersecretion in response both to absorbed metabolites and to cephalic autonomic stimulation. There is receptor evidence for chronic vagal facilitation and lack of sympathetic inhibition of insulin release after VMH lesions (*25*), but it remains to be seen whether this is primary, in parallel to the gastric motor abnormality, or whether it is a neural adaptation to excessive absorption.

Accelerated gastric emptying of food in the rat is not likely to be secondary to hypersecretion of insulin. Insulin injected subcutaneously at doses of 1 U kg^{-1} or less, in the range of amounts secreted by the pancreas (*26*), did not increase the daytime rate of gastric emptying of maintenance chow in the rat (Table 3).

We conclude that hypothalamic obesity and overeating result from deficient tone in gastric and perhaps other motor fields (*9–11, 20, 23, 25*) of the sympathetic autonomic nervous system. Parasympathetic overactivity may be the result of central release of the vagus from sympathetic inhibition. Although theoretical calculations (*14, 27*) indicate that insulin hypersecretion—and the consequent net deposition of a greater proportion of absorbed energy as fat—are necessary to account for the obesity and meal pattern, these calculations cannot distinguish primary autonomic from secondary intestinal facilitation of secretion. In either case, the gastromotor abnormality is quantitatively the most important precondition of excess fat deposition and the hyperphagic pattern of frequent meals (*5, 14*). The slowing of abnormal and even normal gastric emptying should be tested for its contribution to appetite suppression and reduced fat deposition in effective human weight control therapies (*28*).

Table 3. Gastric emptying rates of intact rats early in the light phase after subcutaneous injection of insulin. NS, not significant.

Dose of insulin (U kg^{-1})	n	Emptying rate (g hour^{-1})		Difference*
		Mean	SD	
0	9	0.56	0.09	
0.4	7	0.52	0.09	NS
1.0	9	0.57	0.04	NS
2.0	9	0.78	0.06	$P < 0.01$
10.0	5	0.88	0.06	$P < 0.01$

*Calculated (Dunnett's t test) from saline (zero dose).

References and Notes

1. Not the ventromedial nucleus of the hypothalamus (VMN): R. M. Gold [*Science* **182**, 488 (1973)] showed that the classic VMH syndrome depends on destruction of fibers running alongside the VMN proper. Anodal electrolytic lesions (2 mA, 15 seconds) were used in the work reported here, and their bilateral encroachment on Gold's region was confirmed histologically.
2. J. Le Magnen *et al.*, *J. Comp. Physiol. Psychol.* **84**, 1 (1973); E. Becker and H. R. Kissileff, *Am. J. Physiol.* **226**, 383 (1974).
3. S. P. Grossman, *Physiol. Behav.* **1**, 1 (1966); J. Panksepp, *ibid.* **7**, 381 (1972); B. R. Rabin, *Brain Res.* **43**, 317 (1972).
4. A. C. Sullivan and J. Triscani, in *Hunger*, D. Novin, W. Wyrwicka, G. A. Bray, Eds. (Raven, New York, 1976), p. 115; D. Novin, *ibid.*, p. 357; G. J. Magenson, *ibid.*, p. 473.
5. D. A. Booth and S. P. Jarman, *J. Physiol. (London)* **259**, 501 (1976); D. A. Booth, F. M. Toates, S. V. Platt, in *Hunger*, D. Novin, W. Wyrwicka, G. A. Bray, Eds. (Raven, New York, 1976), p. 127.
6. M. Schmitt, *Am. J. Physiol.* **225**, 1089 (1973).
7. Y. Oomura, in *Hunger*, D. Novin, W. Wyrwicka, G. A. Bray, Eds. (Raven, New York, 1976), p. 145.
8. J. B. Furness and M. Costa, *Rev. Physiol.* **69**, 1 (1974); L. H. Storlien, *Life Sci.* **36**, 505 (1984).
9. C. N. Hales and G. C. Kennedy, *Biochem. J.* **90**, 620 (1964).
10. G. A. Bray, *Proc. Soc. Exp. Biol. Med.* **131**, 1111 (1969).
11. N. J. Rothwell, M. E. Saville, M. J. Stock, *Am. J. Physiol.* **234**, R339 (1982). However, extra thermogenesis in VMH rats could be an artifact of nutritional deficiencies [K. J. McCracken and H. G. Barr, *Br. J. Nutr.* **52**, 192 (1985)] from dietary selection by these finicky animals (*3, 19*).
12. J. E. Cox and T. L. Powley, *Am. J. Physiol.* **240**, E566 (1981).
13. D. A. Booth, *J. Comp. Physiol. Psychol.* **78**, 412 (1972); *Physiol. Behav.* **9**, 199 (1972); S. Nicolaïdis, paper presented at the 26th Congress of the International Union of Physiological Sciences, New Delhi, 4 to 8 July 1974; D. A. Booth, in *Appetite and Food Intake*, T. Silverstone, Ed. (Dahlem Konferenzen, Berlin, 1976), p. 417; M. I. Friedman and E. M. Stricker, *Psychol. Rev.* **83**, 409 (1976).
14. D. A. Booth in *Hunger Models*, D. A. Booth, Ed. (Academic Press, London, 1978), p. 227.

15. J. Le Magnen, *Behav. Brain Sci.* **4**, 596 (1981).
16. J. C. Newman and D. A. Booth, *Physiol. Behav.* **27**, 929 (1981).
17. A rat's food was withheld for the last 4 hours of the dark phase. A chow pellet (diet 422, Heygate and Sons) of known dry weight (~1.8 g) was presented 15 to 60 minutes after the lights came on in the 12:12 light-dark cycle and was consumed within about 10 minutes. The rat (Sprague-Dawley hooded) was weighed and anesthetized 120 minutes after presentation of the pellet, and the stomach was clamped at the pylorus and esophageal junction. Rats that had brain operations were perfused for neurohistology. Water washings of gastric contents were centrifuged twice, and the pellet and supernatants were dried separately to constant weight. Abnormalities in autonomic nervous system control of the stomach can have opposite effects on the emptying of liquids and solids [J. D. Davis and D. A. Booth, *Physiol. Behav.* **12**, 685 (1974)]; furthermore, gastric "dumping" of a load differs from the later main phase of controlled emptying [J. N. Hunt and D. F. Stubbs, *J. Physiol. (London)* **245**, 209 (1975)]. Thus our findings are compatible with the slower emptying of milk in the first 60 seconds after loading in VMH rats [T. Ralph and P. R. Sawchenko, *Brain Res. Bull.* **3**, 11 (1975)].
18. C. M. Brooks and E. F. Lambert, *Am. J. Physiol.* **147**, 695 (1946).
19. N. E. Miller, C. J. Bailey, J. A. F. Stevenson, *Science* **112**, 256 (1950); H. Graff and E. Stellar, *J. Comp. Physiol. Psychol.* **55**, 418 (1962).
20. S. C. Wang, G. Clarke, F. L. Dey, S. W. Ranson, *Am. J. Physiol.* **130**, 81 (1940).
21. F. Rohner *et al.*, *Diabetologia* **13**, 239 (1977).
22. H. R. Berthoud and B. Jeanrenaud, *Endocrinology* **105**, 146 (1979); J. Louis-Sylvestre and J. Le Magnen, *Neurosci. Biobehav. Rev.* **4** (suppl. 1), 13 (1980).
23. H. R. Berthoud *et al.*, *Diabetologia* **20**, 393 (1981).
24. H. S. Sitren and N. R. Stevenson, *J. Nutr.* **110**, 558 (1980).
25. T. Powley [*Psychol. Rev.* **84**, 89 (1977)] and L. A. Campfield, F. J. Smith, and K. F. Fung [in *The Neural Basis of Feeding and Reward*, B. G. Hoebel and D. Novin, Eds. (Haer Institute, Brunswick, ME, 1982), p. 203] reported signs of cholinergic receptor "down-regulation" and adrenergic "up-regulation" in chronic VMH obesity.
26. W. J. Malaisse *et al.*, *J. Lab. Clin. Med.* **71**, 56 (1968); D. A. Booth and S. P. Jarman, *Behav. Biol.* **15**, 159 (1975).
27. Campfield *et al.* (*25*) have made the glucose and fatty acid components of Booth's (*14*) models explicit and added autonomic nervous system control of insulin secretion to the net lipid synthesis-mobilization components. Their calculations confirm the earlier conclusion (*14*) that insulin hypersecretion is necessary in addition to rapid gastric emptying, but they do not establish that the hyperinsulinism is autonomic and primary rather than secondary to rapid absorption and even perhaps to purely metabolic hypertrophy.
28. Rapid gastric emptying has been reported in some clinically obese populations [J. N. Hunt, R. Cash, P. Newland, *Lancet* **1975-II**, 905 (1975); C. Johnson and K. Ekeland, *Gut* **17**, 456 (1976); R. D. Wright *et al.*, *Gastroenterology* **84**, 747 (1983)]. Slow gastric emptying has been reported in the psychopathological self-starvation condition of anorexia nervosa [A. Dubois *et al.*, *Gastroenterology* **77**, 319 (1979)]. The appetite suppressant, antiobesity agent fenfluramine reduces food intake in freely feeding rats primarily by slowing gastric emptying and so extending the satiating effects of a meal [D. A. Booth and D. Stribling, *Proc. Nutr. Soc. (London)* **37**, 181 (1978); R. F. Davies *et al.*, *Physiol. Behav.* **30**, 73 (1983); N. Rowland and P. Carlton, *Life Sci.* **34**, 2495 (1984); D. A. Booth, E. L. Gibson, B. Baker, *Appetite*, in press].

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Postindustrial Melanism in the Peppered Moth

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New data show the geographical pattern of frequency of the melanic morph *carbonaria* of the peppered moth, *Biston betularia*, in 1983–84. These frequencies are compared with data from 1952 to 1970. After 20 years of smoke control, the area of high melanic frequency has contracted to the northeast. The change indicates a disadvantage to *carbonaria* of about 12 percent compared with 20 years ago. Computer simulations, which do not include the assumption of heterozygote advantage, provide a good match to the surface for the period 1952 to 1970, and also the 1983–84 surface. Experiments on visual predation have been criticized as giving unrepresentative estimates of selection but they permit satisfactory simulations to be made.

THE RESPONSE OF THE PEPPERED moth, *Biston betularia*, to environmental changes brought about by industrialization remains one of the most fully documented cases of microevolutionary change. The first survey backed up by quantitative data was published by Kettlewell; it was based on data obtained between 1952 and 1956 and on the use of a variety of moth traps and capture methods. The results were presented in the familiar "pie diagrams" showing the frequencies of the two melanic types, *carbonaria* and *insularia*, and of the typicals. Similar surveys were carried out in 1957 to 1964 and in 1965 to 1970. All three sets of results were listed together by Kettlewell (*1*), and the map of morph frequencies was updated by Sheppard (*2*). A detailed survey was carried out by Clarke and Sheppard (*3*), Whittle *et al.* (*4*), and Bishop (*5*) of the transition from a high melanic frequency in Liverpool to a low frequency in rural northern Wales, an area where *insularia* is rare so that the cline measures the ratio of *carbonaria* to typical. By 1972, smoke control legislation and replacement of old coal-burning housing stock had reduced atmospheric pollution. There was also a drop in *carbonaria* frequency (*6*). In order to provide a baseline for future comparison, a survey was carried out that extended the northern Wales–Liverpool transect to the Pennines east of Manchester (*7*). Data from individual trap sites were mapped with a computer program that interpolates values between points, to provide contours or three-dimensional maps. The surface produced may be altered by varying a smoothing factor, which was chosen to give a good fit to the data available for the northern Wales cline. Over 90 percent *carbonaria* in Cheshire dropped to less than 5 percent in Wales to the southwest of a narrow transition region (*7*).

One of the purposes of the study was to investigate the possibility that heterozygotes for the melanic gene, indistinguishable in appearance from the melanic homozygote, have a greater net fitness than either homozygote, as had been suggested (*1, 8, 9*). It was concluded that the evidence could as well be explained by a migration-selection hypothesis, with the same fitness being ascribed to the two melanic genotypes. The implications of the model were investigated theoretically (*10–12*), and additional evidence was available from breeding experiments (*13*). Using all the available evidence, Mani (*12*) obtained a good fit to the United Kingdom data on melanic morph frequency without the assumption of heterozygote advantage.

Since the early 1970's study of *B. betularia* has been part of the Foundation Year biology program in the Open University. Students are asked to collect moths in standard traps over 5-day periods. Records are credited to the Open University Study Center nearest to their collecting site. Since 1983 specimens of each morph collected have been sent to L. M. Cook for checking. The survey covers most of England and Wales and part of southern Scotland. We present here results for *carbonaria* frequency, based on a total of 1825 moths recorded at 190 locations.

To illustrate morph frequencies, we have used the same computer program and the same smoothing factor that were used in the earlier survey. A spurious sense of continuity is given to point records, but the position of contours is objectively determined once program parameters have been chosen. Frequency surfaces for Kettlewell's survey are

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